

Effect of sex hormones upon hypervitaminosis-A

by

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It has long been known that testosterone can stimulate anabolism and somatic growth [2] and that the catabolic and growth-inhibitory effects of intense overdosage with estradiol can be prevented by testosterone and other testoid compounds [1]. On the other hand, the skeletal lesions induced by lathyrogenic compounds [3] or by an excess of vitamin-A [4, 5] are readily influenced by the somatotrophic hormone and glucocorticoids. In view of these facts, it appeared of interest to establish whether sex hormones could also significantly alter the development of the skeletal changes that are characteristic of hypervitaminosis-A.

MATERIALS AND METHODS

Sixty female Sprague-Dawley rats with an average initial body weight of 100 g (range 95-108 g) were subdivided into six equal groups: *Group I*, untreated controls; *Group II*, vitamin-A; *Group III*, estradiol; *Group IV*, vitamin-A and estradiol; *Group V*, methyltestosterone; *Group VI*, vitamin-A and methyltestosterone.

Vitamin-A was administered in the form of its palmitate in 0.4 ml of sesame oil, by stomach tube. The daily dose level of 20,000 I.U. was given during the first 7 days, the dose being then raised to 30,000 I.U. daily.

Estradiol was injected subcutaneously, in the form of microcrystals, at the daily dose of 250 kg in 0.2 ml of water.

Methyltestosterone was also given subcutaneously in the form of microcrystals, but at the daily dose of 3 mg in 0.2 ml of water, since preliminary experiments had shown that in order to influence the skeletal manifestations of hypervitaminosis-A, larger doses of testoids than of folliculoids are required.

Throughout the experiment, the rats were fed on "Purina Fox Chow". All animals were killed on the 20th day of treatment. Immediately after autopsy, the lower extremity of the right tibia was fixed and simultaneously decalcified in Susa solution for subsequent histologic study of paraffinembedded sections stained with hematoxylin-eosin. Then, the rest of the skeleton was carefully inspected in each case, special attention being given to the femur (as an example of a typical tubular bone) as well as to the scapula and the mandible, which are particularly predisposed to bone absorption during hypervitaminosis-A. The intensity of bone absorption was assessed in terms of an arbitrary-scale of 0 to +++, both macroscopically and microscopically.

RESULTS

Our results are summarized in Table 1.

TABLE 1

Group	Treatment	Final body-weight (g.)	Bone absorption
I	None	160 ± 2.3	0
II	Vit-A	107 ± 8.4	+ to ++
III	Estradiol	108 ± 2.3	0
IV	Vit-A + Estradiol	82 ± 2.4	+++
V	Methyltestosterone	176 ± 3.4	0
VI	Vit-A + Methyltestosterone	141 ± 6.0	0

It is obvious from the mean final body weights that both vitamin-A and estradiol, when given alone, failed to inhibit growth completely but reduced the growth rate to a considerable extent. Combined treatment with vitamin-A and estradiol produced an actual loss in body weight, while methyltestosterone, given simultaneously with vitamin-A, counteracted the growth inhibition of the latter.

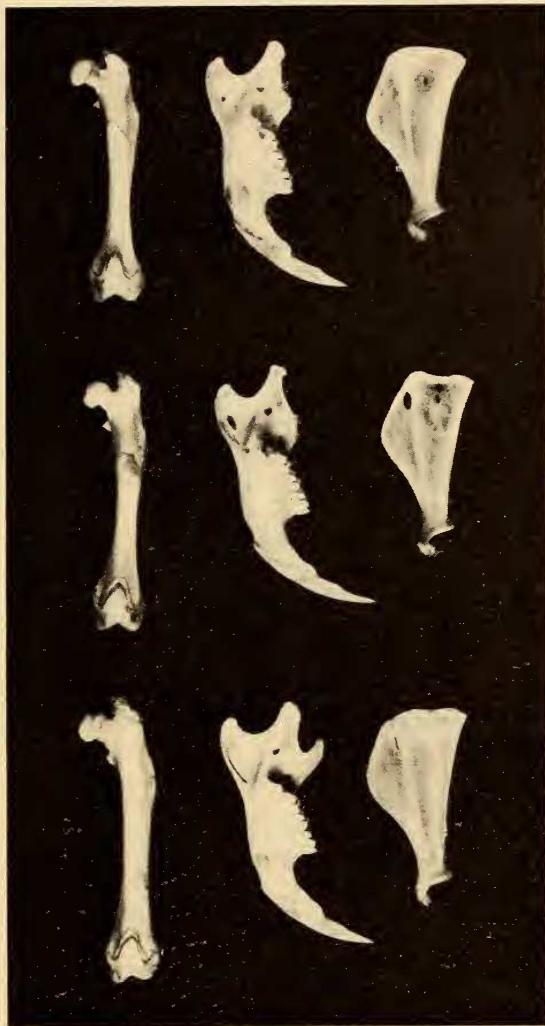


FIG 1.

Scapula, mandible and femur of a rat treated with vitamin-A alone (left), vitamin-A plus estradiol (middle), and vitamin-A plus methyltestosterone (right). Vitamin-A alone caused some thinning of the scapula (dark gray spot) and absorption of the condyloid and particularly of the cornoid process in the mandible. The femur is slightly narrower than normal. This bone absorption is much more pronounced in the animal treated with vitamin-A plus estradiol. Here, there are several actual perforations (black spots) in the scapula and in the mandible. On the other hand, concurrent treatment with methyltestosterone virtually abolished the bone-absorption effect of vitamin-A.

We note, furthermore, that the bone absorption produced by vitamin-A alone (at the dose level at which it was given in these experiments) was only of moderate intensity. However, the skeletal changes caused by the vitamin were considerably accentuated by the concurrent administration of estradiol and inhibited by conjoint treatment with methyltestosterone. These changes are especially obvious in flat bones such as the scapula, or the body of the mandible, but they can also be detected on tubular bones such as the femur (see Fig. 1). Histologic examination of the femora merely confirmed the microscopic findings; the osteoclastic bone absorption characteristic of hypervitaminosis-A is aggravated by estradiol and inhibited by methyltestosterone.

It is obvious from these findings that estradiol can greatly sensitize the skeleton to the characteristic manifestations of hypervitaminosis-A, while methyltestosterone exerts an inverse effect.

SUMMARY

Experiments on albino rats indicate that a moderate excess of vitamin-A, which in itself produces only mild skeletal lesions, results in extraordinarily intense bone absorption if the animals are sensitized to the vitamin by simultaneous treatment with estradiol. On the other hand, the concurrent administration of methyltestosterone counteracts the effect of hypervitaminosis-A upon the skeleton.

At the same time, the anti-anabolic effect of vitamin-A (judged by body weight) is likewise accentuated by estradiol and counteracted by methyltestosterone.

Thus, these observations furnish us with yet another example of a morbid lesion in which a change in the hormonal milieu can abolish, or accentuate, susceptibility to a nonhormonal pathogen.

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